NDA 20-541/S-006 SEP 1 2000

AstraZeneca Pharmaceuticals
Attention: Sandra Bihary, MSN
Executive Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Bihary:

Please refer to your supplemental new drug application dated November 1, 1999, received November 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARIMIDEX® (anastrozole) Tablets.

We acknowledge receipt of your submissions dated November 24, 1999; February 1, 10, 15 and 18; May 31; June 20; July 18 and August 21 and 29, 2000.

This supplemental new drug application provides for the use of ARIMIDEX® (anastrozole) Tablets for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-541/S-006." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your facsimile dated August 31, 2000. This commitment, along with any completion dates agreed upon, is listed below.

> To submit annual safety and survival updates for studies 0027 and 0030 until 75% of the patients are deceased.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

> Division of Drug Marketing, Advertising, and Communications, HFD-42
> Food and Drug Administration
> 5600 Fishers Lane
> Rockville, Maryland 20857

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

> MEDWATCH, HF-2
> FDA
> 5600 Fishers Lane
> Rockville, MD 20857

Please submit one package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Amy Baird, Project Manager, at (301) 594-5771.

Sincerely,

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

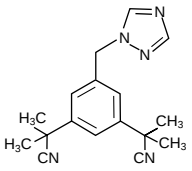
Enclosure

PROFESSIONAL INFORMATION BROCHURE

Arimidex®
anastrozole
TABLETS

DESCRIPTION

ARIMIDEX® (anastrozole) tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is $C_{17}H_{19}N_5$ and its structural formula is:



Anastrozole is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/mL at 25°C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.

Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogen. In post-menopausal women, the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues, such as adipose tissue, with further conversion of estrone to estradiol. Many breast cancers also contain aromatase; the importance of tumor-generated estrogens is uncertain.

Treatment of breast cancer has included efforts to decrease estrogen levels, by ovariectomy premenopausally and by use of anti-estrogens and progestational agents both pre- and post-menopausally; and these interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

Anastrozole is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteriods or aldosterone.

Pharmacokinetics

Inhibition of aromatase activity is primarily due to anastrozole, the parent drug. Studies with radiolabeled drug have demonstrated that orally administered anastrozole is well absorbed into the systemic circulation with 83 to 85% of the radiolabel recovered in urine and feces. Food does not affect the extent of absorption. Elimination of anastrozole is primarily via hepatic metabolism (approximately 85%) and to a lesser extent, renal excretion (approximately 11%), and anastrozole has a mean terminal elimination half-life of approximately 50 hours in postmenopausal women. The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity. The pharmacokinetic parameters are similar in patients and in healthy postmenopausal volunteers. The pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg and do not change with repeated dosing. Consistent with the approximately 2-day terminal elimination half-life, plasma concentrations approach steady-state levels at about 7 days of once daily dosing and steady-state levels are approximately three- to four-fold higher than levels observed after a single dose of ARIMIDEX. Anastrozole is 40% bound to plasma proteins in the therapeutic range.

Metabolism and Excretion: Studies in postmenopausal women demonstrated that anastrozole is extensively metabolized with about 10% of the dose excreted in the urine as unchanged drug within 72 hours of dosing, and the remainder (about 60% of the dose) is excreted in urine as metabolites. Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. Three metabolites of anastrozole have been identified in human plasma and urine. The known metabolites are triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide of anastrozole itself. Several minor (less than 5% of the radioactive dose) metabolites have not been identified.

Because renal elimination is not a significant pathway of elimination, total body clearance of anastrozole is unchanged even in severe (creatinine clearance less than 30 mL/min/1.73m^2) renal impairment, dosing adjustment in patients with renal dysfunction is not necessary (see Special Populations and DOSAGE AND ADMINISTRATION sections). Dosage adjustment is also unnecessary in patients with stable hepatic cirrhosis (see Special Populations and DOSAGE AND ADMINISTRATION sections).

Special Populations:

Geriatric: Anastrozole pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer. No age related effects were seen over the range <50 to >80 years.

Race: Estradiol and estrone sulfate levels were similar between Japanese and Caucasian postmenopausal women who received 1 mg of anastrozole daily for 16 days. Anastrozole mean steady state minimum plasma concentrations in Caucasian and Japanese postmenopausal women were 25.7 and 30.4 ng/mL, respectively.

Renal Insufficiency: Anastrozole pharmacokinetics have been investigated in subjects with renal insufficiency. Anastrozole renal clearance decreased proportionally with creatinine clearance and was approximately 50% lower in volunteers with severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2) compared to controls. Since only about 10% of anastrozole is excreted unchanged in the urine, the reduction in renal clearance did not influence the total body clearance. (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Anastrozole pharmacokinetics have been investigated in subjects with hepatic cirrhosis related to alcohol abuse. The apparent oral clearance (CL/F) of anastrozole was approximately 30% lower in subjects with stable hepatic cirrhosis than in control subjects with normal liver function. However, plasma anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials (see DOSAGE AND ADMINISTRATION), so that no dosage adjustment is needed.

Drug-Drug Interactions: Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with Ki values which were approximately 30 times higher than the mean steady-state C_{max} values observed following a 1 mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by cytochrome P450 2A6 or 2D6 *in vitro*. Administration of a single 30 mg/kg or multiple 10 mg/kg doses of anastrozole to subjects had no effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. Based on these *in vitro* and *in vivo* results, it is unlikely that co-administration of ARIMIDEX 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450 mediated metabolism.

In a study conducted in 16 male volunteers, anastrozole did not alter the pharmacokinetics as measured by C_{max} and AUC, and anticoagulant activity as measured by prothrombin time, activated partial thromboplastine time, and thrombin time of both R- and S-warfarin.

Pharmacodynamics

Effect on Estradiol: Mean serum concentrations of estradiol were evaluated in multiple daily dosing trials with 0.5, 1, 3, 5, and 10 mg of ARIMIDEX in postmenopausal women with advanced breast cancer. Clinically significant suppression of serum estradiol was seen with all doses. Doses of 1 mg and higher resulted in suppression of mean serum concentrations of estradiol to the lower limit of detection (3.7 pmol/L). The recommended daily dose, ARIMIDEX 1 mg, reduced estradiol by approximately 70% within 24 hours and by approximately 80% after 14 days of daily dosing. Suppression of serum estradiol was maintained for up to 6 days after cessation of daily dosing with ARIMIDEX 1 mg.

Effect on Corticosteroids: In multiple daily dosing trials with 3, 5, and 10 mg, the selectivity of anastrozole was assessed by examining effects on corticosteroid synthesis. For all doses, anastrozole did not affect cortisol or aldosterone secretion at baseline or in response to ACTH. No glucocorticoid or mineralocorticoid replacement therapy is necessary with anastrozole.

Other Endocrine Effects: In multiple daily dosing trials with 5 and 10 mg, thyroid stimulating hormone (TSH) was measured; there was no increase in TSH during the administration of ARIMIDEX. ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

Clinical Studies - First Line Therapy in Postmenopausal Women with Advanced Breast Cancer: Two double-blind, well-controlled clinical studies of similar design (0030, a North American study and 0027, a predominately European study) were conducted to assess the efficacy of ARIMIDEX compared with tamoxifen as first-line therapy for hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1021 patients between the ages of 30 and 92 years old were randomized to receive trial treatment. Patients were randomized to receive 1 mg of ARIMIDEX once daily or 20 mg of tamoxifen once daily. The primary end points for both trials were time to tumor progression, objective tumor response rate, and safety.

Demographics and other baseline characteristics, including patients who had measurable and no measurable disease, patients who were given previous adjuvant therapy, the site of metastatic disease and ethnic origin were similar for the two treatment groups for both trials. The following table summarizes the hormone receptor status at entry for all randomized patients in trials 0030 and 0027.

Table 1
Number (%) of subjects

	Trial 0030		Trial 0027	
Receptor status	ARIMIDEX 1 mg (n=171)	Tamoxifen 20 mg (n=182)	ARIMIDEX 1 mg (n=340)	Tamoxifen 20 mg (n=328)
ER+ and/or PR+	151 (88.3)	162 (89.0)	154 (45.3)	144 (43.9)
ER unknown, PR unknown	19 (11.1)	20 (11.0)	185 (54.4)	183 (55.8)

ER = Estrogen receptor
PR = Progesterone receptor

For the primary endpoints, trial 0030 showed ARIMIDEX was at least as effective as tamoxifen for objective tumor response rate. ARIMIDEX had a statistically significant advantage over tamoxifen (p=0.006) for time to tumor progression (see Table 2 and Figure 1). Trial 0027 showed ARIMIDEX was at least as effective as tamoxifen for objective tumor response rate and time to tumor progression (See Table 2 and Figure 2).

Table 2 below summarizes the results of trial 0030 and trial 0027 for the primary efficacy endpoints.

Table 2
Number (%) of subjects

	Trial 0030		Trial 0027	
End Point	ARIMIDEX 1 mg (n=171)	Tamoxifen 20 mg (n=182)	ARIMIDEX 1 mg (n=340)	Tamoxifen 20 mg (n=328)
Time to progression (TTP) Median TTP (months)	11.1	5.6	8.2	8.3
Number (%) of subjects who progressed	114 (67%)	138 (76%)	249 (73%)	247 (75%)
Hazard ratio (LCL)[1]	1.42 (1.15)		1.01 (0.87)	
2-sided 95% CI	(1.11, 1.82)		(0.85, 1.20)	
p-value[2]	0.006		0.920	
Best objective response rate Number (%) of subjects with CR + PR	36 (21.1%)	31 (17.0%)	112 (32.9%)	107 (32.6%)
Odds Ratio (LCL)[3]	1.30 (0.83)		1.01 (0.77)	

CR = Complete Response
PR = Partial Response
CI = Confidence Interval
LCL = Lower Confidence Limit
[1] Tamoxifen:ARIMIDEX
[2] Two-sided Log Rank
[3] ARIMIDEX:Tamoxifen

Figure 1 - Kaplan-Meier probability of time to disease progression for all randomized patients (intent-to-treat) in Trial 0030

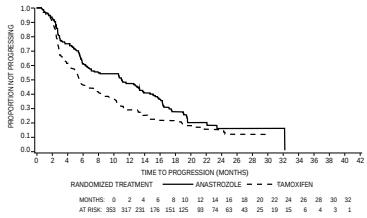
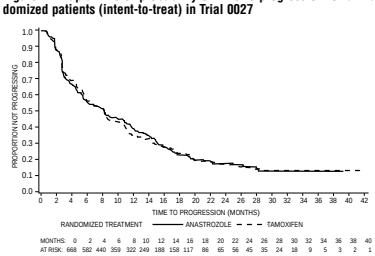


Figure 2 - Kaplan-Meier probability of time to progression for all randomized patients (intent-to-treat) in Trial 0027



Results from the secondary endpoints of time to treatment failure, duration of tumor response, and duration of clinical benefit were supportive of the results of the primary efficacy endpoints. There were too few deaths occurring across treatment groups of both trials to draw conclusions on overall survival differences.

ARIMIDEX® (anastrozole) Tablets

Clinical Studies - Second Line Therapy in Postmenopausal Women with Advanced Breast Cancer who had Disease Progression following Tamoxifen Therapy: Anastrozole was studied in two well-controlled clinical trials (0004, a North American study; 0005, a predominately European study) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. Some of the patients had also received previous cytotoxic treatment. Most patients were ER-positive; a smaller fraction were ER-unknown or ER-negative; the ER-negative patients were eligible only if they had had a positive response to tamoxifen. Eligible patients with measurable and non-measurable disease were randomized to receive either a single daily dose of 1 mg or 10 mg of ARIMIDEX or megestrol acetate 40 mg four times a day. The studies were double-blinded with respect to ARIMIDEX. Time to progression and objective response (only patients with measurable disease could be considered partial responders) rates were the primary efficacy variables. Objective response rates were calculated based on the Union Internationale Contre le Cancer (UICC) criteria. The rate of prolonged (more than 24 weeks) stable disease, the rate of progression, and survival were also calculated.

Both trials included over 375 patients; demographics and other baseline characteristics were similar for the three treatment groups in each trial. Patients in the 0005 trial had responded better to prior tamoxifen treatment. Of the patients entered who had prior tamoxifen therapy for advanced disease (58% in Trial 0004; 57% in Trial 0005), 18% of these patients in Trial 0004 and 42% in Trial 0005 were reported by the primary investigator to have responded. In Trial 0004, 81% of patients were ER-positive, 13% were ER-unknown, and 6% were ER-negative. In Trial 0005, 58% of patients were ER-positive, 37% were ER-unknown, and 5% were ER-negative. In Trial 0004, 62% of patients had measurable disease compared to 79% in Trial 0005. The sites of metastatic disease were similar among treatment groups for each trial. On average, 40% of the patients had soft tissue metastases; 60% had bone metastases; and 40% had visceral (15% liver) metastases.

As shown in the table below, similar results were observed among treatment groups and between the two trials. None of the within trial differences were statistically significant.

Table 3

	ARIMIDEX 1 mg	ARIMIDEX 10 mg	Megestrol Acetate 160 mg
Trial 0004			
(N. America)	(n=128)	(n=130)	(n=128)
Median Follow-up (months)*	31.3	30.9	32.9
Median Time to Death (months)	29.6	25.7	26.7
2 Year Survival Probability (%)	62.0	58.0	53.1
Median Time to Progression (months)	5.7	5.3	5.1
Objective Response (all patients) (%)	12.5	10.0	10.2
Stable Disease for >24 weeks (%)	35.2	29.2	32.8
Progression (%)	86.7	85.4	90.6
Trial 0005			
(Europe, Australia,S. Africa)	(n=135)	(n=118)	(n=125)
Median Follow-up (months)*	31.0	30.9	31.5
Median Time to Death (months)	24.3	24.8	19.8
2 Year Survival Probability (%)	50.5	50.9	39.1
Median Time to Progression (months)	4.4	5.3	3.9
Objective Response (all patients) (%)	12.6	15.3	14.4
Stable Disease for >24 weeks (%)	24.4	25.4	23.2
Progression (%)	91.9	89.8	92.0

*Surviving Patients

More than 1/3 of the patients in each treatment group in both studies had either an objective response or stabilization of their disease for greater than 24 weeks. Among the 263 patients who received ARIMIDEX 1 mg, there were 11 complete responders and 22 partial responders. In patients who had an objective response, more than 80% were still responding at 6 months from randomization and more than 45% were still responding at 12 months from randomization.

When data from the two controlled trials are pooled, the objective response rates and median times to progression and death were similar for patients randomized to ARIMIDEX 1 mg and megestrol acetate. There is, in this data, no indication that ARIMIDEX 10 mg is superior to ARIMIDEX 1 mg.

Table 4

Trials 0004 & 0005 (Pooled Data)	ARIMIDEX 1 mg N=263	ARIMIDEX 10 mg N=248	Megestrol Acetate 160 mg N=253
Median Time to Death (months)	26.7	25.5	22.5
2 Year Survival Probability (%)	56.1	54.6	46.3
Median Time to Progression (months)	4.8	5.3	4.6
Objective Response (all patients) (%)	12.5	12.5	12.3

Objective response rates and median times to progression and death for ARIMIDEX 1 mg were similar to megestrol acetate for women over or under 65. There were too few non-white patients studied to draw conclusions about racial differences in response.

INDICATIONS AND USAGE

ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

CONTRAINDICATIONS

None known.

WARNINGS

ARIMIDEX can cause fetal harm when administered to a pregnant woman. Anastrozole has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about 3/4 and 1.5 times the recommended human dose, respectively, on a mg/m^2 basis). Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about 3/4 and 1/3, respectively, the recommended human dose on a mg/m^2 basis), administered during the period of organogenesis showed that anastrozole increased pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose related in rats. Placental weights were significantly increased in rats at doses of 0.1 mg/kg/day or more.

Evidence of fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), was observed in rats administered doses of 1 mg/kg/day (which produced plasma anastrozole C_{ssmax} and $AUC_{0\text{-}24}$ hr that were 19 times and 9 times higher than the respective values found in healthy postmenopausal humans at the recommended dose). There was no evidence of teratogenicity in rats administered doses up to 1.0 mg/kg/day. In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 1.0 mg/kg/day (about 16 times the recommended human dose on a mg/m^2 basis); there was no evi-

dence of teratogenicity in rabbits administered 0.2 mg/kg/day (about 3 times the recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using ARIMIDEX. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

General: Before starting treatment with ARIMIDEX, pregnancy must be excluded (see WARNINGS).

ARIMIDEX should be administered under the supervision of a qualified physician experienced in the use of anticancer agents.

Laboratory Tests: Three-fold elevations of mean serum gamma glutamyl transferase (GT) levels have been observed among patients with liver metastases receiving ARIMIDEX or megestrol acetate. These changes were likely related to the progression of liver metastases in these patients, although other contributing factors could not be ruled out.

Drug Interactions: (See CLINICAL PHARMACOLOGY) Anastrozole inhibited *in vitro* metabolic reactions catalyzed by cytochromes P450 1A2, 2C8/9, and 3A4 but only at relatively high concentrations. Anastrozole did not inhibit P450 2A6 or the polymorphic P450 2D6 in human liver microsomes. Anastrozole did not alter the pharmacokinetics of antipyrine. Although there have been no formal interaction studies other than with antipyrine, based on these *in vivo* and *in vitro* studies, it is unlikely that coadministration of a 1 mg dose of ARIMIDEX with other drugs will result in clinically significant drug inhibition of cytochrome P450-mediated metabolism of the other drugs.

An interaction study with warfarin showed no clinically significant effect of anastrozole on warfarin pharmacokinetics or anticoagulant activity.

Drug/Laboratory Test Interactions: No clinically significant changes in the results of clinical laboratory tests have been observed.

Carcinogenesis: A conventional carcinogenesis study in rats at doses of 1.0 to 25 mg/kg/day (about 8 to 200 times the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years revealed an increase in the incidence of hepatocellular adenoma and carcinoma and uterine stromal polyps in females and thyroid adenoma in males at the high dose. A dose related increase was observed in the incidence of ovarian and uterine hyperplasia in females. At 25 mg/kg/day, plasma $AUC_{0\text{-}24hr}$ levels in rats were 110 to 125 times higher than the level exhibited in post-menopausal volunteers at the recommended dose. A separate carcinogenicity study in mice at oral doses of 5 to 50 mg/kg/day (about 20 to 200 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years produced an increase in the incidence of benign ovarian stromal, epithelial and granulosa cell tumors at all dose levels. A dose related increase in the incidence of ovarian hyperplasia was also observed in female mice. These ovarian changes are considered to be rodent-specific effects of aromatase inhibition and are of questionable significance to humans. The incidence of lymphosarcoma was increased in males and females at the high dose. At 50 mg/kg/day, plasma AUC levels in mice were 35 to 40 times higher than the level exhibited in postmenopausal volunteers at the recommended dose.

Mutagenesis: ARIMIDEX has not been shown to be mutagenic in *in vitro* tests (Ames and E. coli bacterial tests, CHO-K1 gene mutation assay) or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats).

Impairment of Fertility: Studies to investigate the effect of ARIMIDEX on fertility have not been conducted; however, chronic studies indicated hypertrophy of the ovaries and the presence of follicular cysts in rats administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole C_{ssmax} and $AUC_{0\text{-}24\ hr}$ that were 19 and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). In addition, hyperplastic uteri were observed in chronic studies of female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole C_{ssmax} and $AUC_{0\text{-}24\ hr}$ that were 22 times and 16 times higher than the respective values found in post-menopausal humans at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in humans.

Pregnancy: Pregnancy Category D: (See WARNINGS).

Nursing Mothers: It is not known if anastrozole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIMIDEX is administered to a nursing woman. (See WARNINGS and PRECAUTIONS.)

Pediatric Use: The safety and efficacy of ARIMIDEX in pediatric patients have not been established.

Geriatric Use: In studies 0027 and 0030 about 50% of patients were 65 or older. Patients ≥ 65 years of age had moderately better tumor response and time to tumor progression than patients < 65 years of age regardless of randomized treatment. In studies 0004 and 0005 fifty percent of patients were 65 or older. Response rates and time to progression were similar for the over 65 and younger patients.

ADVERSE REACTIONS

First Line Therapy: ARIMIDEX was generally well tolerated in two well-controlled clinical trials (i.e., Trials 0030 and 0027). Adverse events occurring with an incidence of at least 5% in either treatment group of trials 0030 and 0027 during or within 2 weeks of the end of treatment are shown in Table 5.

Table 5

Body system Adverse event[a]	Number (%) of subjects ARIMIDEX (n=506)		Tamoxifen (n=511)	
Whole body				
Asthenia	83	(16.4)	81	(15.9)
Pain	70	(13.8)	73	(14.3)
Back pain	60	(11.9)	68	(13.3)
Headache	47	(9.3)	40	(7.8)
Abdominal pain	40	(7.9)	38	(7.4)
Chest pain	37	(7.3)	37	(7.2)
Flu syndrome	35	(6.9)	30	(5.9)
Pelvic pain	23	(4.5)	30	(5.9)
Cardiovascular				
Vasodilation	128	(25.3)	106	(20.7)
Hypertension	25	(4.9)	36	(7.0)
Digestive				
Nausea	94	(18.6)	106	(20.7)
Constipation	47	(9.3)	66	(12.9)
Diarrhea	40	(7.9)	33	(6.5)
Vomiting	38	(7.5)	36	(7.0)
Anorexia	26	(5.1)	46	(9.0)
Metabolic and nutritional				
Peripheral edema	51	(10.1)	41	(8.0)
Musculoskeletal				
Bone pain	54	(10.7)	52	(10.2)
Nervous				
Dizziness	30	(5.9)	22	(4.3)
Insomnia	30	(5.9)	38	(5.5)
Depression	23	(4.5)	32	(6.3)
Hypertonia	16	(3.2)	26	(5.1)
Respiratory				
Cough increased	55	(10.9)	52	(10.2)
Dyspnea	51	(10.1)	47	(9.2)
Pharyngitis	49	(9.7)	68	(13.3)
Skin and appendages				
Rash	38	(7.5)	34	(7.6)
Urogenital				
Leukorrhea	9	(1.8)	31	(6.1)

[a]A patient may have had more than 1 adverse event.

ARIMIDEX® (anastrozole) Tablets

Less frequent adverse experiences reported in patients receiving ARIMIDEX 1 mg in either Trial 0030 or Trial 0027 were similar to those reported for second-line therapy.

Based on results from second-line therapy and the established safety profile of tamoxifen, the incidences of 9 prespecified adverse event categories potentially causally related to one or both of the therapies because of their pharmacology were statistically analyzed. No significant differences were seen between treatment groups.

Table 6

Adverse Event Group[a]	Number (n) and Percentage of Patients ARIMIDEX 1 mg (n = 506) n	(%)	NOLVADEX 20 mg (n = 511) n	(%)
Depression	23	(4.5)	32	(6.3)
Tumor Flare	15	(3.0)	18	(3.5)
Thromboembolic Disease[a]	18	(3.5)	33	(6.5)
Venous[b]	5		15	
Coronary and Cerebral[c]	13		19	
Gastrointestinal Disturbance	170	(33.6)	196	(38.4)
Hot Flushes	134	(26.5)	118	(23.1)
Vaginal Dryness	9	(1.7)	3	(0.6)
Lethargy	6	(1.2)	15	(2.9)
Vaginal Bleeding	5	(1.0)	11	(2.2)
Weight Gain	11	(2.2)	8	(1.6)

[a] A patient may have had more than 1 adverse event
[b] Includes pulmonary embolus, thrombophlebitis, retinal vein thrombosis
[c] Includes myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular accident, cerebral ischemia and cerebral infarct

Despite the lack of estrogenic activity for ARIMIDEX, there was no increase in myocardial infarction or fracture when compared with tamoxifen.

Second Line Therapy: ARIMIDEX was generally well tolerated in two well-controlled clinical trials (i.e., Trials 0004 and 0005), with less than 3.3% of the ARIMIDEX-treated patients and 4.0% of the megestrol acetate-treated patients withdrawing due to an adverse event.

The principal adverse event more common with ARIMIDEX than megestrol acetate was diarrhea. Adverse events reported in greater than 5% of the patients in any of the treatment groups in these two well-controlled clinical trials, regardless of causality, are presented below:

Table 7

Number (n) and Percentage of Patients with Adverse Event[†]

Adverse Event	ARIMIDEX 1 mg (n = 262) n	%	ARIMIDEX 10 mg (n = 246) n	%	Megestrol Acetate 160 mg (n = 253) n	%
Asthenia	42	(16.0)	33	(13.4)	47	(18.6)
Nausea	41	(15.6)	48	(19.5)	28	(11.1)
Headache	34	(13.0)	44	(17.9)	24	(9.5)
Hot Flushes	32	(12.2)	29	(10.6)	21	(8.3)
Pain	28	(10.7)	38	(15.4)	29	(11.5)
Back Pain	28	(10.7)	26	(10.6)	19	(7.5)
Dyspnea	24	(9.2)	27	(11.0)	53	(20.9)
Vomiting	24	(9.2)	26	(10.6)	16	(6.3)
Cough Increased	22	(8.4)	18	(7.3)	19	(7.5)
Diarrhea	22	(8.4)	18	(7.3)	7	(2.8)
Constipation	18	(6.9)	18	(7.3)	21	(8.3)
Abdominal Pain	18	(6.9)	14	(5.7)	18	(7.1)
Anorexia	18	(6.9)	19	(7.7)	11	(4.3)
Bone Pain	17	(6.5)	26	(11.8)	19	(7.5)
Pharyngitis	16	(6.1)	23	(9.3)	15	(5.9)
Dizziness	16	(6.1)	12	(4.9)	15	(5.9)
Rash	15	(5.7)	15	(6.1)	19	(7.5)
Dry Mouth	15	(5.7)	11	(4.5)	13	(5.1)
Peripheral Edema	14	(5.3)	21	(8.5)	28	(11.1)
Pelvic Pain	14	(5.3)	17	(6.9)	13	(5.1)
Depression	14	(5.3)	6	(2.4)	5	(2.0)
Chest Pain	13	(5.0)	18	(7.3)	13	(5.1)
Paresthesia	12	(4.6)	15	(6.1)	9	(3.6)
Vaginal Hemorrhage	6	(2.3)	4	(1.6)	13	(5.1)
Weight Gain	4	(1.5)	9	(3.7)	30	(11.9)
Sweating	4	(1.5)	3	(1.2)	16	(6.3)
Increased Appetite	0	(0)	1	(0.4)	13	(5.1)

[†]A patient may have more than one adverse event.

Other less frequent (2% to 5%) adverse experiences reported in patients receiving ARIMIDEX 1 mg in either Trial 0004 or Trial 0005 are listed below. These adverse experiences are listed by body system and are in order of decreasing frequency within each body system regardless of assessed causality.

Body as a Whole: Flu syndrome; fever; neck pain; malaise; accidental injury; infection

Cardiovascular: Hypertension; thrombophlebitis

Hepatic: Gamma GT increased; SGOT increased; SGPT increased

Hematologic: Anemia; leukopenia

Metabolic and Nutritional: Alkaline phosphatase increased; weight loss

Mean serum total cholesterol levels increased by 0.5 mmol/L among patients receiving ARIMIDEX. Increases in LDL cholesterol have been shown to contribute to these changes.

Musculoskeletal: Myalgia; arthralgia; pathological fracture

Nervous: Somnolence; confusion; insomnia; anxiety; nervousness

Respiratory: Sinusitis; bronchitis; rhinitis

Skin and Appendages: Hair thinning; pruritus

Urogenital: Urinary tract infection; breast pain

Vaginal bleeding has been reported infrequently, mainly in patients during the first few weeks after changing from existing hormonal therapy to treatment with ARIMIDEX. If bleeding persists, further evaluation should be considered.

During clinical trials and postmarketing experience joint pain/stiffness has been reported in association with the use of ARIMIDEX.

The incidences of the following adverse event groups potentially causally related to one or both of the therapies because of their pharmacology, were statistically analyzed: weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness. These six groups, and the adverse events captured in the groups, were prospectively defined. The results are shown in the table below.

Table 8

Number (n) and Percentage of Patients

Adverse Event Group	ARIMIDEX 1 mg (n = 262) n	(%)	ARIMIDEX 10 mg (n = 246) n	(%)	Megestrol Acetate 160 mg (n = 253) n	(%)
Gastrointestinal Disturbance	77	(29.4)	81	(32.9)	54	(21.3)
Hot Flushes	33	(12.6)	29	(11.8)	35	(13.8)
Edema	19	(7.3)	28	(11.4)	35	(13.8)
Thromboembolic Disease	9	(3.4)	4	(1.6)	12	(4.7)
Vaginal Dryness	5	(1.9)	3	(1.2)	2	(0.8)
Weight Gain	4	(1.5)	10	(4.1)	30	(11.9)

More patients treated with megestrol acetate reported weight gain as an adverse event compared to patients treated with ARIMIDEX 1 mg ($p<0.0001$). Other differences were not statistically significant.

An examination of the magnitude of change in weight in all patients was also conducted. Thirty-four percent (87/253) of the patients treated with megestrol acetate experienced weight gain of 5% or more and 11% (27/253) of the patients treated with megestrol acetate experienced weight gain of 10% or more. Among patients treated with ARIMIDEX 1 mg, 13% [33/262] experienced weight gain of 5% or more and 3% [6/262] experienced weight gain of 10% or more. On average, this 5 to 10% weight gain represented between 6 and 12 pounds.

No patients receiving ARIMIDEX or megestrol acetate discontinued treatment due to drug-related weight gain.

ARIMIDEX® (anastrozole) Tablets

OVERDOSAGE

Clinical trials have been conducted with ARIMIDEX, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of ARIMIDEX that results in life threatening symptoms has not been established. In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m^2 basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage).

In an oral acute toxicity study in the dog the median lethal dose was greater than 45 mg/kg/day.

There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because ARIMIDEX is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

First-line Therapy: The dose of ARIMIDEX is one 1 mg tablet taken once a day. Treatment with ARIMIDEX should continue until tumor progression is evident.

Second-line Therapy: The dose of ARIMIDEX is one 1 mg tablet taken once a day.

Patients treated with ARIMIDEX do not require glucocorticoid or mineralocorticoid replacement therapy.

Patients with Hepatic Impairment: (See CLINICAL PHARMACOLOGY.) Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Although clearance of anastrozole was decreased in patients with cirrhosis due to alcohol abuse, plasma anastrozole concentrations stayed in the usual range seen in patients without liver disease. Therefore, no changes in dose are recommended for patients with mild-to-moderate hepatic impairment, although patients should be monitored for side effects. ARIMIDEX has not been studied in patients with severe hepatic impairment.

Patients with Renal Impairment: No changes in dose are necessary for patients with renal impairment.

Use in the Elderly: No dosage adjustment is necessary.

HOW SUPPLIED

White, biconvex, film-coated tablets containing 1 mg of anastrozole. The tablets are impressed on one side with a logo consisting of a letter "A" (upper case) with an arrowhead attached to the foot of the extended right leg of the "A" and on the reverse with the tablet strength marking "Adx 1". These tablets are supplied in bottles of 30 tablets (NDC 0310-0201-30).

Store at controlled room temperature, 20°-25°C (68°-77°F) [see USP].

AstraZeneca

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